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TTC post-processing is beneficial for functional MRI at low magnetic field: a comparative study at 1 T and 3 T

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Abstract This study aimed to broaden the diagnostic possibilities of low-field MRI systems (i) by examining the feasibility of functional MRI of human brain activation at 1 T, and (ii) by assessing its reliability in comparison with acquisitions at 3 T. Eight subjects were studied at 1 T and 3T using standard echo-planar-imaging sequences at 3-mm isotropic spatial resolution. Paradigms included silent word generation, sequential finger-to-thumb opposition, and passive finger movements. Image post-processing was carried out either with statistical parametric mapping (SPM5, single-subject and group analysis) or with a two-threshold correlation (TTC, single-subject analysis only) analysis. Single-subject analysis with SPM5 resulted in 3–5 times more activated pixels at 3 T than at 1 T in the examined Broca and sensorimotor regions. By comparison, the TTC single-subject analysis yielded the same amount of activated pixels at 3 T and 1 T. Moreover, this number was identical to that obtained with SPM at 3 T. The group analysis with SPM5 resulted in very similar numbers of activated pixels at both field strengths. The present findings suggest that a field strength of 1 T combined with adequate post-processing allows for reliable functional MRI studies of human brain activation. High-field advantages are therefore best invested in higher spatial resolution.

Keywords Functional MRI · Low field · High field · Comparative study · Post-processing

Introduction

Functional magnetic resonance imaging (fMRI) allows for a noninvasive visualization of cortical and subcortical networks in human brain that are engaged in information processing in relation to the performance of a specific task or the perception of an external (or internal) stimulus. Accordingly, such methods may prove invaluable for the diagnosis of functional deficits in a wide variety of patients with brain disorders. Because the MRI-detectable hemodynamic response to a change in neural activity depends on the microscopic magnetic susceptibility changes that are induced by changes in the absolute concentration of deoxyhemoglobin, its sensitivity is commonly expected to increase with the strength of the static magnetic field. In fact, comparative studies using echo-planar imaging (EPI) at a high and low field [1–5] all indicated that a higher field strength is unquestionably superior, such that the authors of a successful functional MRI study at 1 T even felt tempted to disqualify their own sound results as "somewhat controversial" [6]. However, the increased sensitivity to macroscopic susceptibility artifacts at higher fields is certainly disadvantageous for many clinical conditions. For instance, hippocampal activations in response to a mental

navigation paradigm used in epilepsy [7] are often hampered by pronounced EPI signal losses and geometric distortions in the vicinity of air-filled cavities and sinuses [1, 8]. Furthermore, neurosurgical patients who underwent a preceding brain operation may have defects in skull bone which also result in severe susceptibility artifacts compromising EPI of residual neighboring tissue—the obvious target of functional MRI studies in these cases.

So far, only a limited number of low-field functional MRI studies have been reported in the literature, for example, see [6, 9–12]. The aim of our work was to evaluate the feasibility of functional MRI at 1 T using relatively simple experimental conditions that are readily available for routine clinical examinations. The results were compared with corresponding data obtained for the same group of subjects on a high-end 3-T MRI system.

Two post-processing strategies were compared: statistical parametric mapping (SPM) [13] and the two-threshold correlation (TTC). Though SPM is elegantly designed for the statistically trained and experienced researcher, a potential drawback of the method is its complexity. As a consequence, SPM applications require substantial knowledge with the potential risk that the rank-and-file user may be misguided to produce inadequate results. A detailed description of the statistics used in SPM can be found in the literature [13]; thus its detailed presentation is beyond the scope of this study.

An alternative fMRI data processing method has been established [14] that emerges as a rather simple data-driven approach originally motivated by detailed experimental observations and physiologic considerations [15]. The method is referred to as two-threshold correlation (TTC) and has evolved during the analysis of several thousands of fMRI data sets acquired in multiple studies by our laboratory. TTC is based on correlation coefficient (CC) maps that are thresholded individually by estimating the noise distribution underlying the distribution (or histogram) of correlation coefficients of the actual fMRI acquisition. In fact, studies without any stimulation (Null experiment) demonstrated that the width of a corresponding CC distribution may be affected by alterations of the hemodynamic responsiveness (‘arousal’), respiration, perfusion, flow-induced tissue pulsations, or motions. Because the basic form of these distributions is adequately described by a Gaussian curve, true brain activations (i.e., voxels representing paradigm-associated fMRI signal alterations) may be easily identified: the CC histogram of an fMRI study emerges as the sum of a dominating noise distribution and a second much smaller distribution of activated voxels with high positive (or negative) CC values. In comparison with methods based on a single threshold (e.g., SPM), the TTC method employs two probabilistic thresholds for their separation: a high value for the identification of highly significant activations and a lower value for limiting the iterative addition of directly neighboring voxels to these centers. The approach ensures both specificity and sensitivity for defining the spatial extent of significant activation spots.

A successful demonstration of reliable low-field functional MRI studies would extend the diagnostic possibilities for a wide spectrum of neurological/neurosurgical patients who only have access to low-field MRI systems, mainly in second-world and developing countries. In addition, interventional MRI systems that usually operate at a low field strength may equally benefit from the establishment of suitable approaches.

Materials and methods

Subjects and paradigms

Eight healthy normal volunteers (male, right-handed, mean age 31±4 years) participated in the study. Handedness was examined by the Edinburgh inventory test [16]. Approval by the Institutional Review Board was obtained and all subjects gave written informed consent before each examination.

Mapping of eloquent language and sensorimotor areas was accomplished with use of a block design, alternating active and passive periods each lasting for 50 s. The paradigms involved (i) seven cycles of internal word generation (generating words beginning with a given letter) and rest [17, 18], (ii) five cycles of sequential finger-to-thumb opposition (SFO) and motor rest [19], and (iii) five cycles of a passive finger movement (investigator moved the fingers of the volunteer according to ref. [20]) and motor rest. During SFO the subjects’ cooperation was visually monitored and for passive movements a similar frequency of 1–2 Hz was chosen. Subsequent to a word generation paradigm subjects were interrogated with respect to their performance.

MRI

Low-field MRI examinations were conducted on a clinical system operating at 42-MHz proton frequency (Siemens Magnetom Harmony, Erlangen, Germany). A standard Siemens circularly polarized head coil was used for signal excitation and detection. Functional studies employed an EPI sequence as supplied by the manufacturer with the following parameters: TR/TE=2,500 ms/80 ms, flip angle 90°, receiver bandwidth 752 Hz, FOV 192×192 cm and matrix 64×64 yielding 3×3 mm in-plane resolution, and 16 sections with a thickness of 3 mm and 1-mm gap.

Corresponding high-field MRI examinations were conducted at 123-MHz proton frequency (Siemens Trio, Erlangen, Germany). Excitation was performed with the body coil, while signal reception was achieved with an eight-channel head coil. Again, a standard EPI sequence was applied with the following parameters: TR/TE=

2,500 ms/36 ms, flip angle 80°, receiver bandwidth 1,184 Hz, and 20 sections. Other parameters were identical to those used at 1 T.

Data processing

At both field strengths a retrospective motion correction was performed as offered by the manufacturer. Significant activations were identified by two different statistical evaluations using either a single-threshold *t* test (SPM) or a two-threshold correlation analysis (TTC). In the first approach, a single-subject and group analysis of all 1-T and 3-T data were performed with SPM5 [13], applying a low statistical threshold of $p<0.05$ (family-wise error (FEW) corrected [21]). Concurrent activation of a cluster of at least ten neighboring voxels was assumed to represent a true spot of activation and a 6-s-long delay in hemodynamic response was applied similar to TTC analysis. In the group analysis only, the images were subjected to a spatial Gaussian filter of 5-mm full width at half maximum and normalized to the standard Talairach space [22].

Alternatively, all data sets were evaluated on a single-subject basis using a two-threshold correlation (TTC) analysis [14, 15]. Briefly, in a first step, activation maps were calculated as maps of correlation coefficients with use of a boxcar reference function derived from the task protocol and shifted by 6 s to account for the delayed hemodynamic response. Voxels are accepted as activated if their correlation coefficients exceed the 99.99th percentile rank of the noise distribution estimated on an individual basis from the actual measurement. The noise distribution represents the histogram of correlation coefficients as, for example, obtained in the absence of a stimulus and has been found to be a symmetric function centered around zero. The noise distribution underlying an actual measurement may be estimated from the histogram by fitting only its central portion, that is, low coefficients that do not refer to high positive (or negative) stimulus-related correlations. In a second step, neighboring pixels of such activation centers are iteratively added as long as their correlation coefficients exceed the 95th percentile rank of the noise distribution. Thus, the upper and lower thresholds of the TTC approach correspond to *p* values <0.0001 and <0.05, respectively. The correlation coefficients corresponding to these *p* values can be rigorously determined from the Gaussian-fit of the correlation coefficient distribution [14, 15]. In comparison with SPM, the method is rather data-driven and does not require subjective thresholding either in the *t* score or the number of concurrently activated neighboring pixels. A particular strength of the method is the ability to account for intertrial variability in the noise distribution that may be caused by residual motions or systemic physiological changes unrelated to the task [15]. Further, the TTC method minimizes the problem of false-positive activations because any accepted activation is based on a central spot (i.e., at least one pixel) with a correlation coefficient that corresponds to a *p* value $<$ 0.0001. The lower threshold of 0.05 only applies to the outer boundary of such highly significant centers.

Region of interest analyses of activation volumes (i.e., number of activated pixels) and MRI signal intensity time courses were performed in the Broca and sensorimotor cortex in all subjects and examinations individually, based on the TTC results. The locations of these regions were identified by an overlay of respective Brodmann areas using freeware software (MRIcro) in each examined MRI section. In the target regions, the analysis was based on the largest activation cluster including neighboring slices.

Statistical analysis

Data processing and statistical analysis was performed with MatLab 6.5 software. One-tailed, paired *t* test was applied to identify significant differences (i.e., $p<0.05$) in the number of activated voxels. The signal-to-noise ratio (SNR) of the images was determined by dividing the mean of all intensities originating from the brain by the standard deviation of all intensities outside the head (i.e., air).

Results

Despite considerable intrasubject and intersubject variability in the activation maps—regardless of field strength and paradigm—the present results yielded consistent findings with respect to field strength and post-processing strategy. The upper parts of Fig. 1 show the activation maps of a single subject obtained for the word generation paradigm. While at 1 T the single-subject TTC analysis (Fig. 1, top rows) yielded more activated pixels in the Broca area than SPM (Fig. 1, middle rows), this example revealed approximately the same amount of activation at 3 T for both methods. This latter observation also holds true for an SPM group analysis averaging all word generation data sets across subjects (Fig. 1, bottom rows).

Figure 2 displays activation maps for executing the SFO task. Again, at 1 T the single-subject TTC analysis resulted in much more extended activations in the primary sensorimotor cortex and supplementary motor cortex than the single-subject SPM approach. At 3 T the activation maps for both methods were equivalent as were the SPM group analyses at both field strengths. Representative results for the passive finger movement paradigm in another subject are demonstrated in Fig. 3. In this case the single-subject TTC analysis yielded even more activated voxels at 1 T than at 3 T (similar to Fig. 2), whereas the single-subject SPM approach again showed much less activation at the lower field strength. In agreement with the other paradigms, the SPM group analyses were almost undistinguishable at both field strengths.

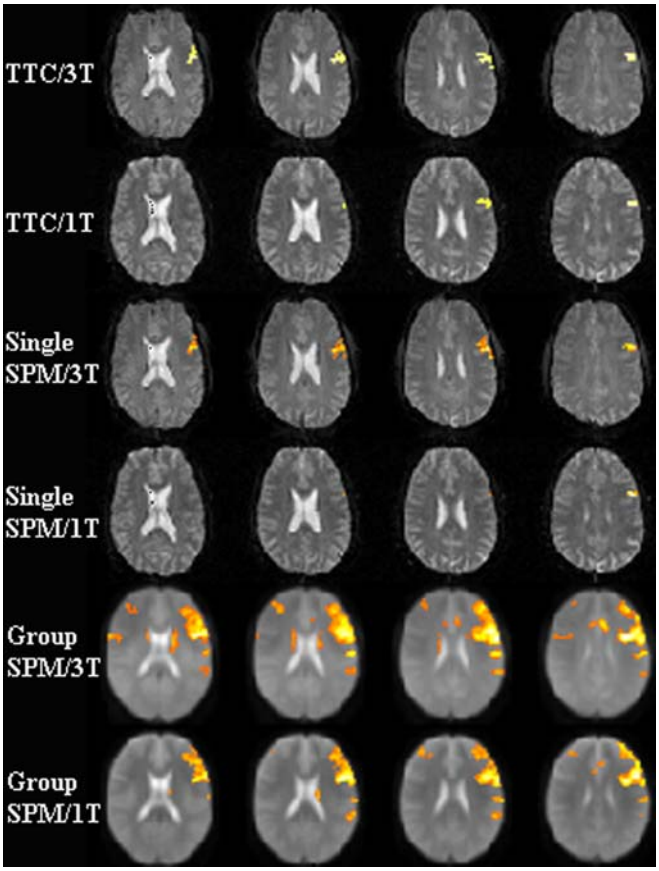

Fig. 1 Activation maps of a single subject obtained for silent word generation at 1 T and 3 T and for different analysis methods. *Top rows* single-subject two-threshold correlation analysis, *middle rows* single-subject SPM analysis, and *bottom rows* SPM group analysis (eight subjects). At 1 T the TTC approach yielded more activated voxels than single-subject SPM

The mean SNR of all images at 3 T (265±46) was 4.5 times larger than at 1 T (59±7) because of both the larger spin polarization and an improved radiofrequency coil design. The corresponding MRI signal intensities of all activated pixels in the Broca area and sensorimotor cortex are shown in Fig. 4 as mean curves averaged across subjects. The magnitudes of the signal changes for word generation (3%) and SFO (3.5%) were found to be identical at both field strengths. For passive finger movement the mean signal change in the sensorimotor region was 4.5% at 1 T and 6% at 3 T. Table 1 summarizes the mean number of activated voxels in the Broca and sensorimotor regions. For all paradigms, the TTC and SPM single-subject analyses at 3 T gave similar results, whereas the SPM approach failed to reveal similar activations at 1 T but resulted in about threefold lower numbers of activated voxels. The single-subject TTC approach, however, identified a similar number of activated voxels for all paradigms at both field strengths. Similar results for the SPM approach could only be obtained when applying it to a group analysis.

Discussion

Low-field MRI systems tend to spread mostly in neurosurgery and render possible fMRI or diffusion tensor imaging (DTI) in the operating room. Despite some successful demonstrations of feasibility of intraoperative fMRI [23–25], appropriate fMRI sequences (fluid-attenuated inversion recovery [26] or gradient echo) and mostly post-processing strategies at low magnetic field require more investigation to cope with inherently low signal-to-noise ratio.

So far, published reports comparing functional MRI of human brain activation at different field strengths [1–5] unanimously conclude that a higher field is preferable. Unfortunately, however, at least part of these studies involved the use of special radiofrequency coils [2]; or special MRI sequences, not generally available for routine clinical work, were applied [3, 5]. The purpose of our study was to make a fair comparison by completely relying on commercial coils and standard EPI sequences. Moreover,

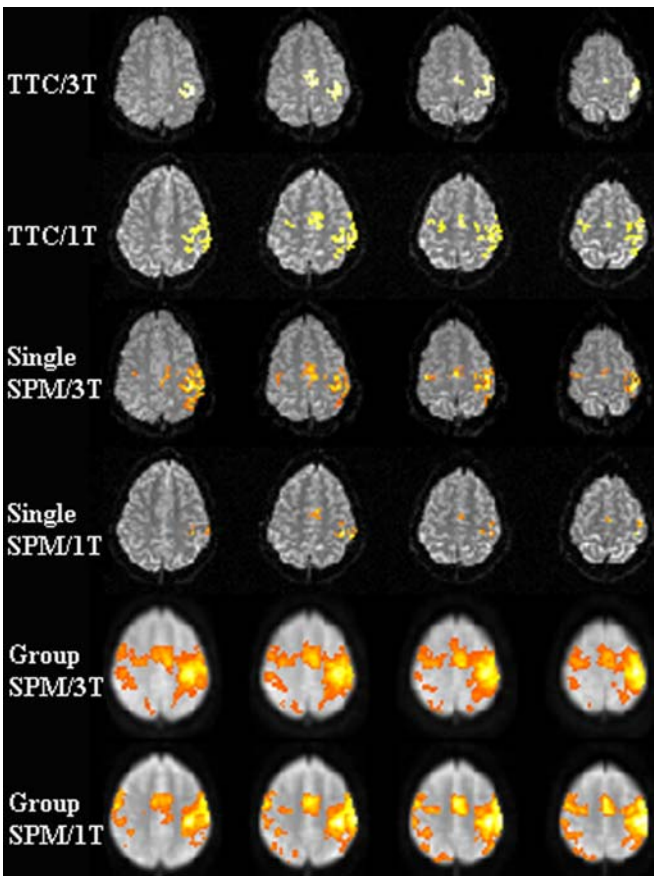

Fig. 2 Activation maps of a single subject obtained for sequential finger opposition at 1 T and 3 T and for different analysis methods. *Top rows* single-subject two-threshold correlation analysis, *middle rows* single-subject SPM analysis, and *bottom rows* SPM group analysis (eight subjects). As in Fig. 1, the TTC approach yielded more activated voxels than single-subject SPM at the lower field strength

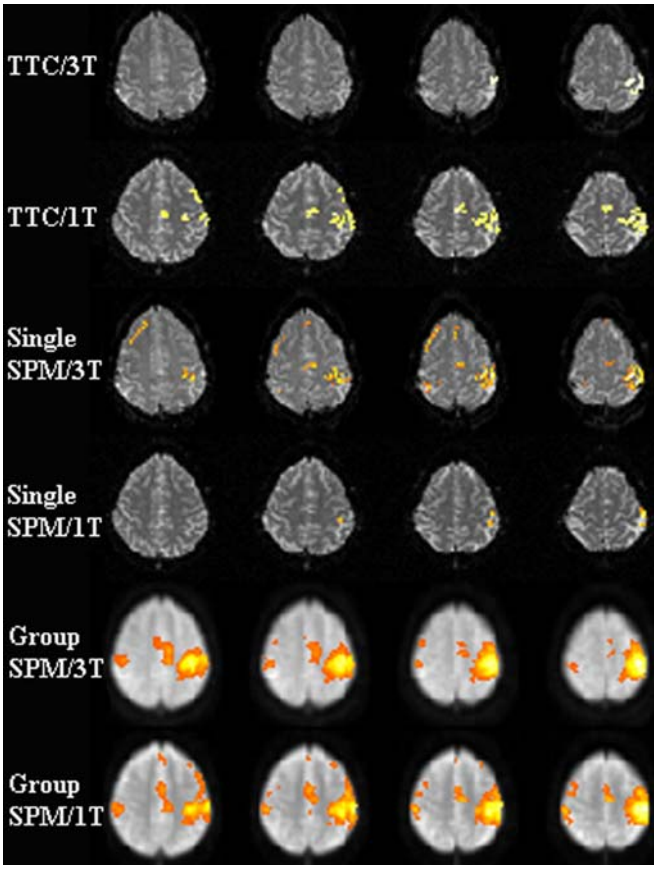

Fig. 3 Activation maps of a single subject obtained for passive finger movement at 1 T and 3 T and for different analysis methods. *Top rows* single-subject two-threshold correlation analysis, *middle rows* single-subject SPM analysis, and *bottom rows* SPM group analysis (eight subjects). As shown in Figs. 1 and 2, the TTC approach yielded more activated voxels than single-subject SPM at the lower field strength

experiments were performed at a typical spatial resolution and for clinically relevant paradigms that map eloquent brain areas.

Not surprisingly, the data resulted in similar percent MRI signal changes in response to word generation and sequential finger opposition at 1 T and 3 T. Only a moderate increase was observed for passive finger movements at 3 T. It is well known that—for a given voxel size—the sensitivity to (microscopic) susceptibility differences primarily depends on the gradient echo time. Thus, the increase in sensitivity to susceptibility differences at a higher magnetic field strength—for a given echo time—may well be compensated for by increasing the echo time at a lower field. This effect has also previously been reported by comparing functional MRI studies at 1.5 T and 3 T [4, 5]. For instance, Krüger et al. [5] measured similar BOLD signal changes for a visual and motor task at 1.5 T and 3 T. The large intrasubject variability of fMRI data [27] is another well-known feature and is obvious on Figs. 1–3. Despite extreme examples such as a subject who produced more activation at 1 T than at 3 T (Fig. 2, TTC), our results yielded consistent findings with respect to the post-processing strategies.

As a novel finding, the present results clearly indicate the influence of the method chosen for post-processing and in particular for the statistical evaluation of significant activations. While both the single-subject TTC and SPM analyses yielded similar numbers of activated voxels at 3 T, the SPM approach failed in detecting such activations at 1 T. In fact, the number of activated voxels was reduced by about a factor of 3. On the contrary, the TTC approach readily identified similar activations at both field strengths. This discrepancy may be best explained by the use of two physiologically justified thresholds that reflect the individual noise in the distribution of correlation coefficients for

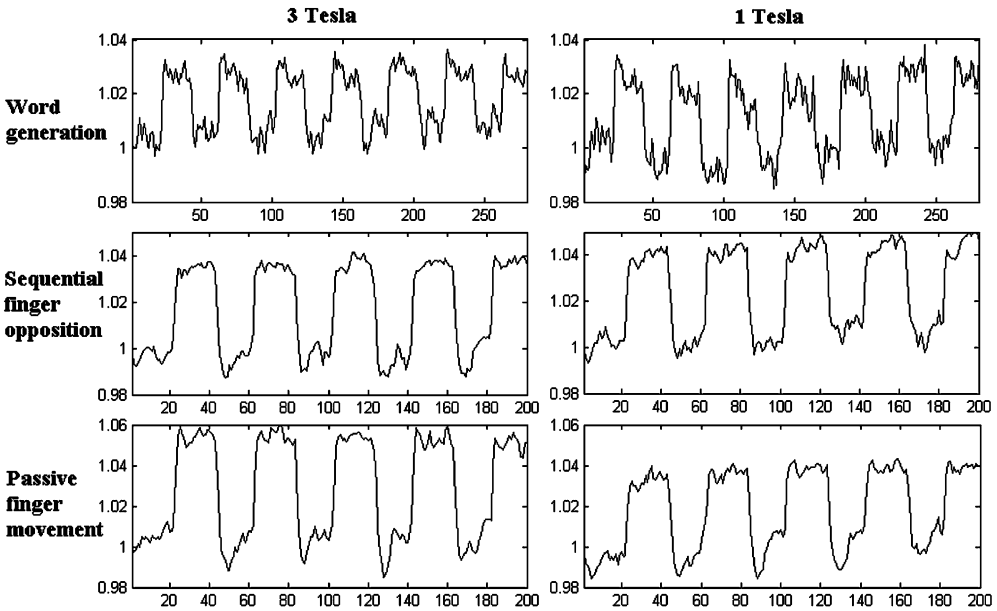

Fig. 4 Mean MRI signal intensity time courses (eight subjects) in selected regions of interest for silent word generation, sequential finger opposition, and passive finger movement at 1 T and 3 T. While silent word generation and sequential finger opposition resulted in similar percent changes at both field strengths, passive finger movement elicited moderately larger signal changes at 3 T

Table 1 Numbers of activated voxels in Broca and sensorimotor regions

	3 T	1 T	3 T/1 T
Word generation			
SS[1] TTC[2]	40±43	38±24*	1.05
SS SPM[3]	39±38	11±8	3.55
Group SPM	567	421	1.35
Sequential finger opposition			
SS TTC	176±117	157±42**	1.12
SS SPM	150±67	52±25	2.88
Group SPM	781	764	1.02
Passive finger movement			
SS TTC	131±58	135±51**	0.97
SS SPM	133±38	41±24	3.24
Group SPM	598	580	1.03

[1]SS single-subject analysis,
[2]*TTC* two-threshold correlation analysis,
[3]*SPM*statistical parametric mapping
*$p<0.005$ and **$p<0.0005$ in comparison with single-subject SPM

each trial and subject. In other words, TTC activation maps take into account the intrasubject variability not identified by SPM (compare Fig. 2, first four rows). The concept of two thresholds accounts for the fact that highly significant activation centers or nuclei (pixels identified by a high threshold) are usually surrounded by directly neighboring pixels that are also activated but at a somewhat lower statistical significance (area delineation above a lower threshold). This combined strategy appears to be much more robust than the single threshold employed by SPM in situations of limited SNR. Together with suitably adjusted echo times, it obviously compensates to a large degree for a lower functional contrast-to-noise than principally available at higher fields. The lack of similar observations in previously published reports may possibly be explained by the fact that—to the best of our knowledge—all such studies were analyzed with SPM or other methods using only a single threshold. It should be emphasized that the gain in the number of activated pixels for TTC as compared with SPM is not the result of the putative generation of more false-positive activations. Instead, the opposite is true, as TTC uses a low statistical threshold of $p<0.05$ exclusively for limiting the extent of activations that are originally identified with a threshold of $p<0.0001$, whereas SPM relies on $p<0.05$ throughout. It should be also noted that statistical threshold of $p<0.05$ is differently defined in SPM and TTC. Otherwise the same number of activated pixels would occur in both post-processing strategies.

The present findings offer two more consequences. Firstly, they again demonstrate the particular strength of the SPM approach for group analyses, and secondly, they lead to the recommendation that the good SNR at higher fields is best exploited by improving the spatial resolution. Or conversely, limitations of functional MRI studies at a low magnetic field strength are to be expected in those cases that require higher spatial resolution and/or better sensitivity for the detection of subtle MRI responses to more sophisticated cognitive paradigms.

Conclusion

In conclusion, adequate post-processing allows for functional MRI of human brain activation on a routine clinical instrument at a low magnetic field strength of 1 T. The approach is feasible, sensitive, and—compared with data obtained at 3 T—reliable. This observation is in accordance with the few published studies performed at 1 T [6, 9–12]. Similar functional contrast, i.e., MRI signal changes in response to a functional challenge, may be obtained at different field strengths by adjusting the gradient echo time, while keeping the spatial resolution constant. The use of a suitable statistical strategy may largely compensate for low SNR.

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